International Journal of Pharmaceutics, 60 (1990) 203–217
Elsevier

IJP 02046

The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure *

M.J. Pikal, S. Shah, M.L. Roy and R. Putman

Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, IN 46285 (U.S.A.)

(Received 1 August 1989)
(Modified version received 16 November 1989)
(Accepted 17 November 1989)

Key words: Freeze drying; Lyophilization; Secondary drying; Drying rate; Glassy materials

Summary

Secondary drying involves removal of water which did not freeze. This report emphasizes the phenomenological description of the effects of temperature and chamber pressure on the kinetics of drying. A crystalline solute (mannitol) and two amorphous solutes (moxalactam di-sodium and povidone) were selected for study. Drying kinetics were determined gravimetrically using a vacuum microbalance and by Karl Fischer assay of vials sealed at selected times during secondary drying experiments conducted in a laboratory scale freeze dryer. The main observations may be summarized as follows: (1) the water content decreases rapidly during the first few hours of drying and then appears to approach a plateau level of residual water which far exceeds the equilibrium water content calculated from the desorption isotherm data and the measured partial pressure of water in the drying chamber; (2) this plateau level of water sharply decreases as the drying temperature is increased; (3) the drying rate increases as the product specific surface area increases; and (4) variations in chamber pressure (0–0.2 mmHg) and dried product thickness have little or no effect on drying rate. We conclude that the rate-limiting mass transfer process for drying an amorphous solid is either evaporation at the solid/vapor interface or diffusion in the solid, probably the former. The 'plateau level kinetics' appears to be consistent with amorphous particle size heterogeneity superimposed on a simple model based on Fickian diffusion with rate controlling surface evaporation.

Introduction

The freeze drying process may be divided into three stages: freezing, primary drying, and secondary drying. Primary drying refers to that stage where ice is being transformed into vapor by sublimation while secondary drying refers to removal of unfrozen water. The unfrozen water may be adsorbed on the surface of the crystalline product or is in the solute phase either as hydrate water in a crystalline hydrate or dissolved in an amorphous solid to form a solid solution, the latter being the most common. Secondary drying begins locally when all ice has been removed from that region. Thus some secondary drying proceeds simultaneously with primary drying in different regions of the same sample. Low levels of residual water are not attained until primary drying is completed, and the water activity in the sample is reduced to a low value. Normally, secondary drying continues for some time after the conclusion

Correspondence: M.J. Pikal, Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, IN 46285, U.S.A.

* Presented, in part, at the 39th National Meeting of the APHA Academy of Pharmaceutical Sciences, Vol. 15, no. 2, Oct. 20–24, 1985, Minneapolis, MN, Abstract no. 108.

of primary drying, and frequently the secondary drying stage is defined, in an operational sense, as the time after all ice has been removed. Throughout the remainder of this report, we use this operational definition.

Secondary drying is usually carried out at shelf temperature of 25 °C or higher, which frequently is well above the shelf temperature used in primary drying. Current practice also employs very low chamber pressures during secondary drying even though this practice may cause problems with transfer of volatile stopper components to the product (Pikal and Lang, 1978). This practice is based on the notion that high chamber pressure retards the rate of secondary drying. While this notion has some foundation in the older literature (Robson and Rowe, 1960; Saravacos and Stinchfield, 1967; King, 1968; Mellor, 1978), none of these studies dealt with products, containers, and freeze dryers representative of pharmaceutical freeze drying systems.

While primary drying of pharmaceutical products has been studied in some detail (Nail, 1980; Pikal et al., 1983a, 1984; Pikal, 1985), suitable physical chemical data on secondary drying of pharmaceutical systems is lacking. This report describes the results of a series of secondary drying experiments with emphasis on the phenomenological description of the effects of temperature and chamber pressure on the kinetics. The effects of product thickness and specific surface area were also investigated. A crystalline solute (mannitol) and two amorphous solutes (moxalactam disodium formulated with 12% mannitol and povidone) were selected for study. Both drying kinetics and sorption kinetics were determined gravimetrically using a vacuum microbalance. Drying kinetics were also obtained by Karl Fischer assay of vials sealed at selected times using a laboratory freeze dryer.

Experimental

Materials

Povidone (USP, K-90), and mannitol (USP) were used as received, and the moxalactam (purity > 96%) was obtained as raw material (Eli Lilly). The water was distilled (water for injection, Eli Lilly), and all solutions were prepared by weight. The vials were 10 cm^3 tubing vials with a 20 mm neck finish and an inner diameter of 2.2 cm (Wheaton). The stoppers were 'slotted' freeze drying stoppers (West Co., no. 1816 rubber stock).

Apparatus and procedures

Water sorption isotherms Sorption isotherm measurements were made gravimetrically using a microbalance procedure (Pikal et al., 1983b). Here, a small sample in a quartz pan on a microbalance is dried to zero water content at 50 °C and high vacuum, 10^{-6} mmHg, (i.e., dried until the mass is independent of time). The sample is then brought to the temperature of interest, T_1, and is exposed to water vapor from a water or ice sample at temperature T_2 until constant weight is reached. The entire experiment is carried out at near zero background air pressure.

Microbalance studies The apparatus was essentially the same as previously described (Pikal et al., 1983a) except for the sample cell. The cell used for secondary drying studies was a 'finned' aluminum heat exchanger with a 0.8 cm cylindrical hole to contain the sample, similar in design to the cell used for primary drying studies on the microbalance (Pikal et al., 1983a), but with a much larger sample capacity (0.5 ml vs 13 μl). Preliminary studies showed that a black anodized finish produced an unacceptable high background effect during sorption isotherm studies, due to sorption of water by the anodized finish, so the secondary drying cell was not anodized. This modification has the effect of reducing the heat transfer characteristics of the cell, resulting in a slight deviation from isothermal operation during the first 30 min of a sorption or drying experiment. The cell temperature as measured by the thermocouple probe (Pikal et al., 1983a) would typically be, at a maximum, about 2 °C warmer than the thermostat during early sorption or 2 °C cooler during early drying. The magnitudes of these temperature shifts were largest for the runs at 25 °C (maximum shifts of 2 °C) and were essentially independent of background air pressure. We assume, as was found in sublimation of pure ice

with the primary drying cell (Pikal et al., 1983a), that the corresponding shifts in product temperature are only slightly greater than those measured in cell temperature, but we do not have data to verify this assumption.

The sample used for secondary drying studies was prepared by first freeze drying a moxalactam di-sodium/mannitol solution (0.5 ml, 30% total solids, mannitol is 12% of solids) directly in the secondary drying cell at a product temperature of $-25\,^{\circ}C$ during primary drying (collapse temperature is $-22\,^{\circ}C$) and a final temperature of $50\,^{\circ}C$ in secondary drying. Constant weight at $50\,^{\circ}C$ was used as the operational definition of complete removal of water. The dried sample at selected temperatures was then exposed to controlled partial pressure of water in the absence of air to determine the sorption kinetics. The source of water vapor was a temperature controlled sample of water or ice in 'vapor contact' with the sample (Pikal et al., 1983b). After the sample equilibrated to the appropriate water content (7% unless noted otherwise) as demonstrated by constant weight, the drying kinetics were studied by exposing the sample to the pumping system. For the experiments at high vacuum ($\approx 10^{-6}$ mmHg), a diffusion pump backed by a mechanical pump was used. For the experiments at 0.2 mmHg, the diffusion pump was not used, and a controlled air leak was used to maintain a constant background air pressure of 0.2 mmHg. Data reported are means of two replicate experiments. The differences between replicate data normally ranged from about $\pm 0.05\%$ water at low residual water ($\approx 0.5\%$) to about $\pm 0.15\%$ at high water content ($> 5\%$).

Vial studies The secondary drying studies conducted on samples in vials were carried out using our laboratory freeze dryer (Pikal et al., 1983a, 1984). The condenser was operated during all experiments ($-55\,^{\circ}C$). This dryer is equipped with a movable 'arm' which allows stoppers on selected vials to be fully closed during a run without disturbing the vacuum in the drying chamber. This feature allows vials to be closed, and drying for those vials quenched, at selected times during the secondary drying experiment. Vapor composition in the drying chamber and partial pressure of water were evaluated as previously described (Pikal et al., 1984).

Samples for use in secondary drying studies were prepared by first filling the 10 cm^3 vials with the appropriate volume of aqueous solution (8 or 4 ml), and then freeze drying. The freeze drying procedures were as follows: (1) mannitol; the filled vials were equilibrated with a shelf preset to $0\,^{\circ}C$. The shelf was then lowered to $-35\,^{\circ}C$ over approx. 0.5 h and then held at $-35\,^{\circ}C$ for 2 h prior to initiation of drying. Primary drying was carried out at product temperatures between -30 and $-20\,^{\circ}C$, and secondary drying at a product temperature of $30\,^{\circ}C$ for several hours. The freeze dried product was highly crystalline (X-ray powder pattern and microscopic examination under polarized light). (2) Formulated moxalactam disodium; the vials were equilibrated with a shelf pre-cooled to about $-8\,^{\circ}C$. No freezing took place during this stage. The shelf was then lowered to $-22\,^{\circ}C$ over approx. 0.5 h and held at that temperature overnight, thereby freezing the product. The shelf was then lowered to $-40\,^{\circ}C$ and held at that temperature for 1 h. Primary drying was carried out at least $3\,^{\circ}C$ below the collapse temperature ($-22\,^{\circ}C$). The conditions used for secondary drying varied, but normally involved a final product temperature of about $30\,^{\circ}C$ for at least 8 h. (3) Povidone; filled vials were equilibrated with a shelf pre-cooled to about $10\,^{\circ}C$. The shelf was then lowered to $-15\,^{\circ}C$, held at that temperature for 0.5 h, lowered to about $-40\,^{\circ}C$, and held at $-40\,^{\circ}C$ for about 1 h. Primary drying was carried out at a product temperature of about $-25\,^{\circ}C$ (collapse temperature $\approx -17\,^{\circ}C$) while secondary drying was generally carried out at a product temperature of $30\,^{\circ}C$ for at least 8 h.

After freeze drying, samples contained in vials were brought to a uniform water content (normally $\approx 7\%$) by equilibrating with a saturated salt solution of the appropriate water activity in a vacuum desiccator *. After loading a group of vials into the laboratory dryer, the secondary drying experiment was initiated, and at each time point (1, 2, 3, 4, 6 h), three vials were stoppered while in the dryer to quench drying. Water con-

* See footnote, p. 206.

tent was determined after the secondary drying experiment by Karl Fischer titration. The standard error of the mean (3 samples) was generally about $\pm 0.1\%$ H_2O for formulated moxalactam di-sodium and povidone samples and about $\pm 0.05\%$ H_2O for mannitol samples.

Results

Drying kinetics: Time dependence

An example of drying kinetics over the whole of the freeze drying process for moxalactam di-sodium is given by Fig. 1. The 'rate of H_2O loss' curve was calculated from measured pressure differentials across the stopper as previously described (Pikal, et al., 1983a). The corresponding product temperature, measured at the bottom center of the vial, shows a sharp increase in temperature at around 17 h, indicating that most (or all) of the ice has been removed from that vial. Coincident with this increase in product temperature, the rate of water loss decreases sharply but does not drop to zero immediately. Non-zero rate of water loss between 17 and 24 h is consistent with rapid removal of unfrozen water in the early stages of secondary drying, but could also reflect, in part, removal of trace quantities of ice not in thermal contact with the temperature sensor (thermocouple). Product temperature and rate of water loss data refer to the same vial (the 'instrumented' vial). Temperature-time profiles in other vials containing thermocouples are similar and show sharp increases in product temperature within about 1 hour of that shown by the instrumented vial in Fig. 1. The 'H_2O content' curve refers to mean residual water in vials not containing temperature sensors. Since the product temperature-time curves will not be identical for all vials, the time axis in Fig. 1 is only an approximation for the water content curve. Because of this approximation, water contents are highly variable at the 19 and 20 h time points ($\approx \pm 5$ to $\pm 2\%$). In spite of this limitation, the water content curve is a valid semi-quantitative representation of the mean water content during secondary drying under the conditions of the experiment. Note that the residual water about 2 h after the 'sharp increase in product temperature' is very high (20%) but decreases very sharply with increasing time even when the

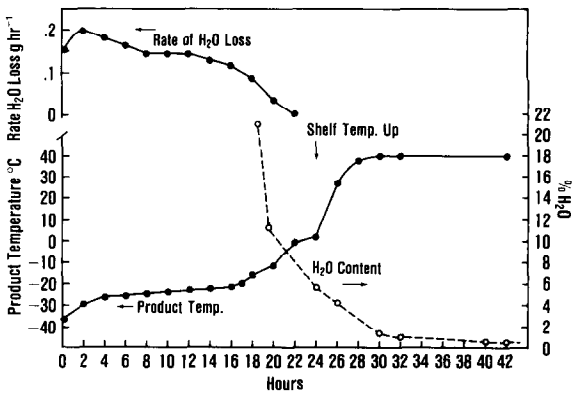

Fig. 1. The rate of water loss and levels of residual water during freeze drying: moxalactam di-sodium formulated with 12% mannitol in aqueous solution at 30% solids. The 10-ml tubing vials had a solution fill depth of 1 cm. The chamber pressure was 0.05 mmHg. (○) Residual water content in weight percent.

* The physical state of solute-water system at 7% water content prepared by absorption of water (our procedure) is not necessarily identical to the corresponding system at 7% water prepared by desorption (i.e., as in a freeze drying run) if the sample exhibits hysteresis in its water sorption-desorption isotherm. While we find that moxalactam di-sodium does not exhibit hysteresis, povidone does show a small degree of hysteresis at the temperatures relevant to our studies (MacKenzie and Rasmussen, 1972). Our procedure assumes that the effects of such hysteresis, if significant, at least do not invalidate the application of the generalizations developed in this research to a freeze drying process. It should also be noted that while the samples generated by absorption of water to 7% water are uniform in water content throughout the sample, a sample brought to 7% water during a freeze drying process may have some heterogeneity in water content. One might speculate that the water content of the material at the top of the cake may be slightly lower than the water content at the bottom of the cake. Our experimental procedure implicitly assumes that such heterogeneity, if it exists, does not greatly affect the drying kinetics. This assumption is justified retrospectively by our observations that drying kinetics are not significantly affected by cake depth (i.e., material at the top of the cake dries roughly at the same rate as material at the bottom) and that the drying rate is faster at higher water content (i.e., any heterogeneity will quickly be leveled out as drying proceeds.

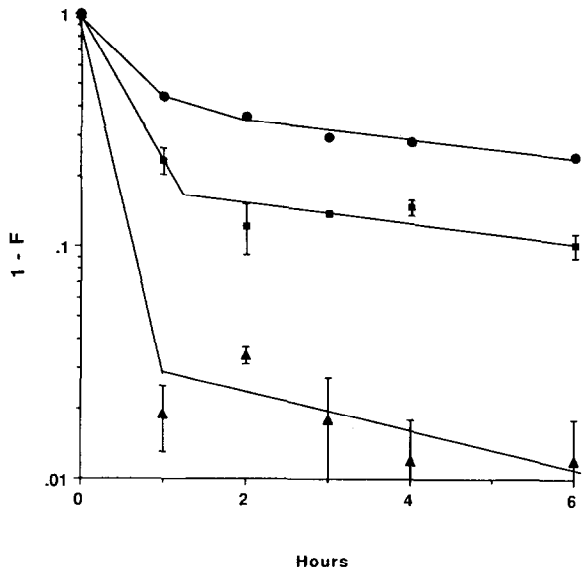

Fig. 2. Secondary drying kinetics for vial freeze dried products from 5% aqueous solutions. Product temperature, 18 °C; chamber pressure, 0.2 mmHg; fill depth, 1 cm. The variable, F, is the fractional attainment of equilibrium, which for drying is defined as the water removed at time t divided by the initial water content. (●) Formulated moxalactam di-sodium; (■) povidone; (▲) mannitol.

product temperature is very low (≈ -10 to 0 °C). At the 24 h time point, the shelf temperature was increased from the setting used for primary drying (−8 °C) to +50 °C to carry out the remainder of the secondary drying. Note that after the water content decreases below about 2%, the rate of further drying is very slow, even though the product has reached the terminal temperature of about 40 °C [due to radiative heat transfer characteristic of this freeze dryer (Pikal et al., 1984), the product temperatures are not exactly equal to the corresponding shelf temperatures].

Secondary drying kinetics for freeze dried products in vials are compared in Fig. 2. Error bars represent the standard errors of the means and are used when the standard error exceeds the size of the plotting symbol. Here, previously freeze dried samples were adjusted to the same initial water content (normally $\approx 7\%$), and secondary drying was conducted at constant chamber pressure (0.2 mmHg) and constant product temperature (18 °C). Water content is expressed in terms of fractional attainment of equilibrium, F. Thus, the ordinate, $1-F$, is a normalized measure of residual water and is defined as the fraction of initial water remaining in the sample at the time indicated. This format was chosen to be consistent with diffusion theory (Crank, 1956). The glass transition temperatures for both povidone (MacKenzie and Rasmussen, 1972) and formulated moxalactam di-sodium (Pikal and Shah, 1990) containing 7% water are about 55 °C. Thus, all secondary drying studies are conducted well below the glass transition temperatures of the solids. Note that, for each product, the normalized residual water content decreases sharply during the first hour of drying and decreases very slowly between 1 and 6 h, apparently asymptotically approaching a 'plateau level' of residual water.

Table 1 compares the measured and calculated equilibrium levels of residual water in moxalactam di-sodium and povidone after 6 h of secondary drying at 18 °C. The secondary drying kinetics for these experiments (not shown) appears similar to the corresponding kinetics shown in Fig. 2. Equilibrium levels of residual water were calculated from the observed partial pressure of water in the drying chamber and the water desorption isotherm for povidone (MacKenzie and Rasmussen, 1972) or moxalactam di-sodium (Fig. 3). The observed residual water contents are obviously greatly in excess of the corresponding equilibrium values.

TABLE 1

Deviation of residual moisture from equilibrium values at the 6 h time point (drying runs at a chamber pressure of 0.2 mmHg and a product temperature of 18 °C; product thickness, 2.2 cm)

Compound	SSA [a] (m^2/g)	$P(H_2O)$ [b] (mmHg)	Residual H_2O (6 h) (wt%)	Equilibrium H_2O (wt%)
Povidone [c]	2.5	0.011	0.96	0.04
Moxalactam di-sodium [d]	0.3	0.009	3.2	0.08

[a] Product specific surface area measured by BET analysis of nitrogen adsorption isotherms.
[b] Partial pressure of water in the drying chamber at 6 h.
[c] Freeze dried from a 5% aqueous solution.
[d] Containing 12% mannitol. Freeze dried from an aqueous solution containing 30% solids.

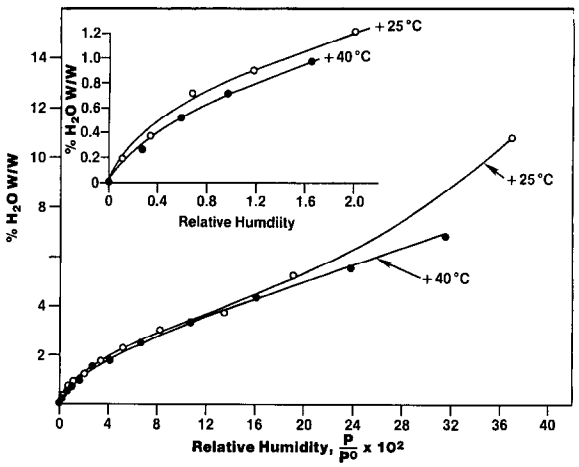

Fig. 3. Water sorption isotherms for freeze dried moxalactam di-sodium formulated with 12% mannitol. The inset shows the low relative humidity range in more detail. (○) 25°C; (●) 40°C.

Results of two 'interrupted drying' experiments with povidone are summarized by Fig. 4. Here, secondary drying was conducted according to the usual procedure, but at the end of the 6 h drying period, the dryer was vented with dry air, and all stoppers were seated to seal each vial. The samples were then allowed to 'equilibrate' internally during a delay period, after which the stoppers were re-positioned, and secondary drying was resumed. These experiments were designed as a check for one possible mechanism for the 'plateau effect' kinetics (Fig. 2). If the diffusion coefficient of water in the amorphous phase decreases sharply as the water content decreases during early secondary drying, the diffusion coefficient of water near the amorphous solid/vapor interface (where the water concentration is lowest) will become very small, thus retarding the flux of water through the impermeable or 'hardened' surface region. It can be shown that such a model does give the type of kinetics observed in this research (Crank, 1956). However, during the delay period, diffusion of water to the surface region should allow the concentration of water to become relatively uniform throughout the thickness of the amorphous 'particles' which form the porous cake. When drying is resumed, the water diffusion coefficient in the surface region will be much larger than immediately before interruption, and one should observe a faster drying rate in the first few hours after the delay than in the last few hours before the delay, although the drying rate would be lower than at the start of the experiment due to the lower water concentration. However, although the experiment is not definitive, the data (Fig. 4) do not appear to support this 'surface hardening' model. While the higher water content at the 7 h time point (after the delay) than at the 6 h time point for the 18°C run complicates the interpretation of this experiment, the slopes of the water content vs. time curves are essentially the same before and after the delay for both experiments.

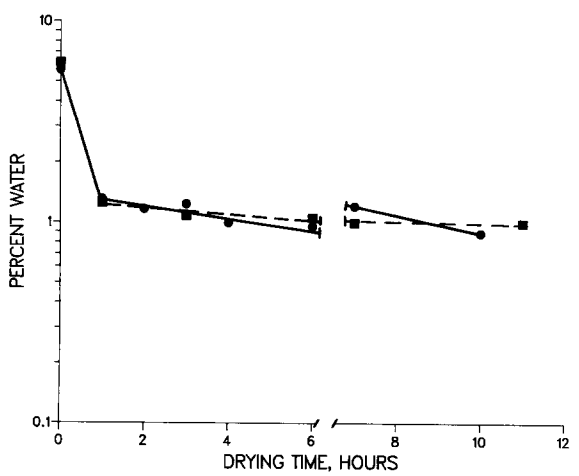

Fig. 4. Results of interrupted drying tests with povidone: a check for formation of an impermeable skin at the solid/vapor interface. Dried solids were produced by vial freeze drying 5% aqueous solutions. (●———●) 2 cm cake depth, 18°C, 0.2 mmHg, 24 h delay; (■- - - - -■) 1 cm cake depth, 2°C, 0.05 mmHg, 40 h delay.

Effects of chamber pressure and product temperature

The effect of chamber pressure on secondary drying kinetics is illustrated by Fig. 5 (vial data) and Fig. 6 (microbalance data). No systematic effect of chamber pressure on drying kinetics is evident from the data shown (Figs. 5 and 6). The small differences shown between low pressure and high pressure data points do not reproduce at the two other temperatures studied in the vial and microbalance experiments (data not shown) and

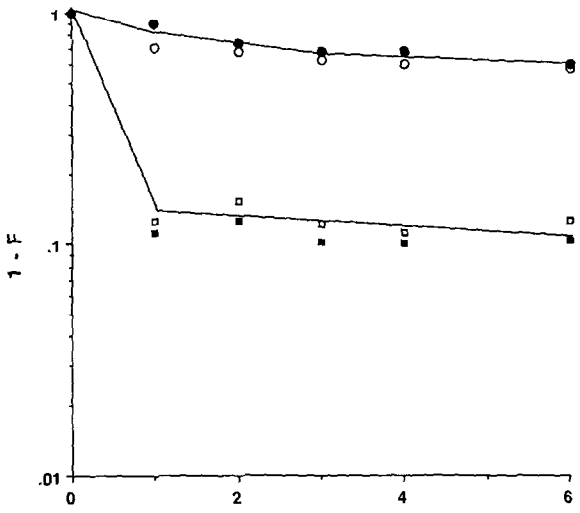

Fig. 5. Effect of chamber pressure on drying kinetics: vial results. (○, □) 0.05 mmHg chamber pressure; (●, ■) 0.2 mmHg chamber pressure; (○, ●) secondary drying of formulated moxalactam di-sodium at 2°C, moxalactam di-sodium prepared from 30% solutions with 1 cm fill depths; (□, ■) secondary drying of povidone at 36°C, povidone prepared from 5% solutions with 2 cm fill depths.

are simply a result of small systematic experimental error. Mannitol data likewise show no systematic pressure effect (data not shown).

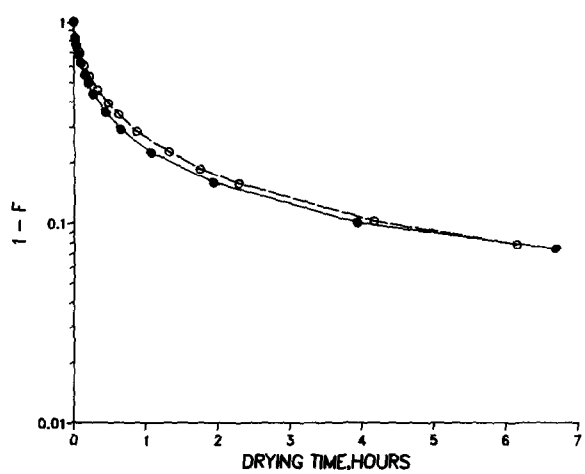

Fig. 6. Effect of chamber pressure on formulated moxalactam di-sodium drying kinetics at 25°C: microbalance results. (○) $\approx 10^{-6}$ mmHg; (●) 0.2 mmHg.

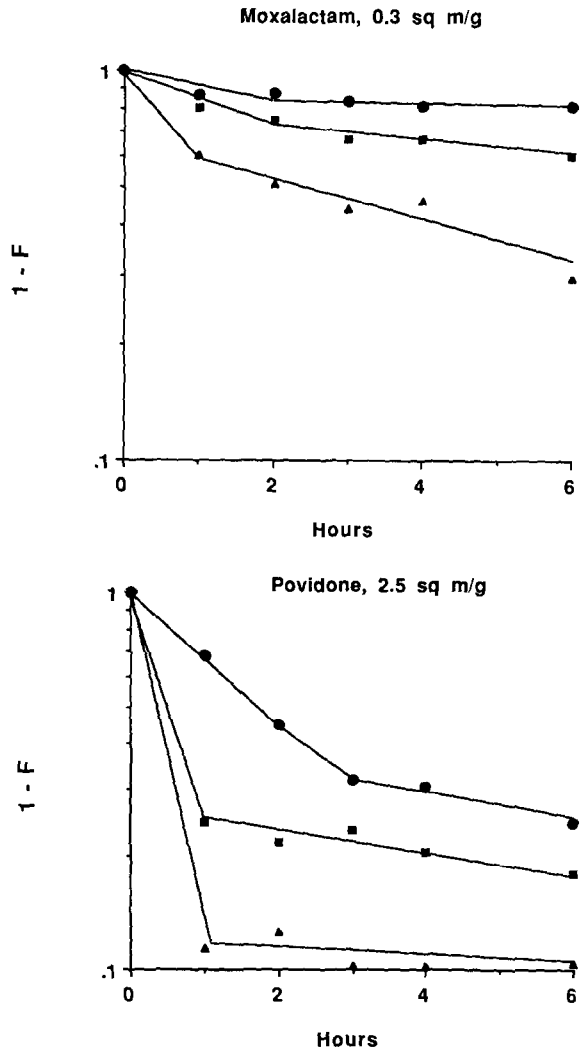

Fig. 7. Effect of temperature on drying kinetics: vial results for 2 cm cake thicknesses with chamber pressures of 0.2 mmHg. Initial water contents: 5.1%. (Upper plot) Formulated moxalactam di-sodium from a 30% solution; (lower plot) povidone. (●) 2°C, (■) 18°C, (▲) 36°C.

The temperature dependence of drying kinetics for vial samples of formulated moxalactam di-sodium and povidone are illustrated in Fig. 7 while the temperature dependence of sorption and desorption kinetics for microbalance experiments with moxalactam di-sodium is shown in Fig. 8. Microbalance drying data in Fig. 8 represent the means of low and high pressure experiments. Clearly, drying is much faster and plateau levels of

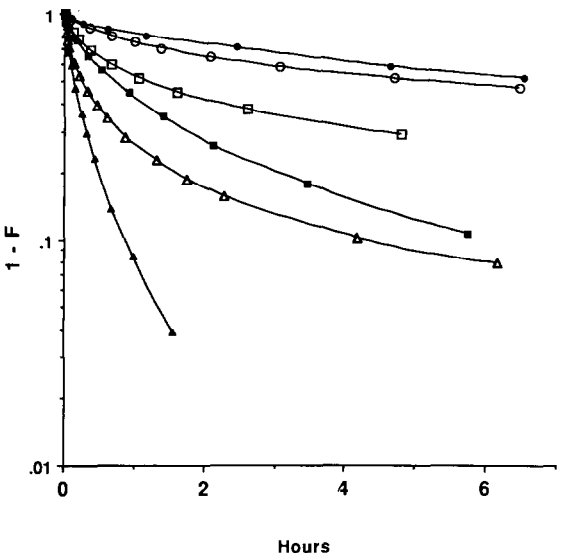

Fig. 8. Effect of temperature on drying kinetics and sorption kinetics: microbalance results for formulated moxalactam di-sodium of 7% initial water content. (○, □, △) Sorption kinetics, (●, ▲, ■) drying kinetics. (○, ●) −20°C, (□, ■) 0°C, (△, ▲) 25°C.

residual water are much lower at higher temperature. Additional vial data for povidone and formulated moxalactam di-sodium at low chamber pressure and 1 cm cake thickness (data not shown) show the same qualitative temperature effects as illustrated by Fig. 7. Corresponding results for mannitol (not shown) do not show the same dramatic temperature effect. Drying curves for mannitol at 2 and 36°C are essentially the same as shown in Fig. 2 for 18°C. Residual water levels are only about 0.1% higher at 2°C than at 36°C. Of course, there may be a significant temperature effect for mannitol at times less than one hour.

During preliminary experiments, microbalance drying of moxalactam di-sodium was studied at temperatures up to 39°C. The sample was crushed vial freeze dried pure moxalactam di-sodium with an initial water content of about 10% (freeze dried from a 25% aqueous solution). The glass transition temperature measured by DSC (Pikal et al., 1990) is 65°C. Data were obtained at −21, 25 and 39°C, with kinetic results being semi-quantitatively the same at the corresponding temperatures as the data given in Fig. 8. Values of $1 - F$ at 6 h were: 0.4 (−21°C), 0.11 (25°C), and 0.04 (39°C). The times required to achieve a $1 - F$ value of 0.1, denoted $t_{0.1}$, were: $t_{0.1} \gg 24$ h (−21°C), $t_{0.1} = 8.5$ h (25°C), and $t_{0.1} = 2.0$ h (39°C). The temperature dependence of $t_{0.1}$ is obviously quite high. Assuming the reciprocal of $t_{0.1}$ (a 'drying rate') shows Arrhenius temperature dependence between 25 and 39°C, one calculates a temperature dependence equivalent to an 'activation energy' of 19 kcal/mol.

Effects of product characteristics

Several simple analyses of mass transport via diffusion (Crank, 1956) result in the drying kinetics expressed by the 'normalized residual water content', $1 - F$, being independent of initial water content of the sample. Data in Fig. 9 show that, at least for formulated moxalactam di-sodium, this prediction of simple diffusion theory is only a first approximation. As the initial water content varies from 2.7 to 7%, values of $1 - F$ show a slight but experimentally significant decrease at all time values.

We generally find that the specific surface area of a freeze dried amorphous sample decreases as the concentration of aqueous solution being freeze dried increases. Also, specific surface area normally increases as the degree of supercooling increases and freezing rate increases, so increased

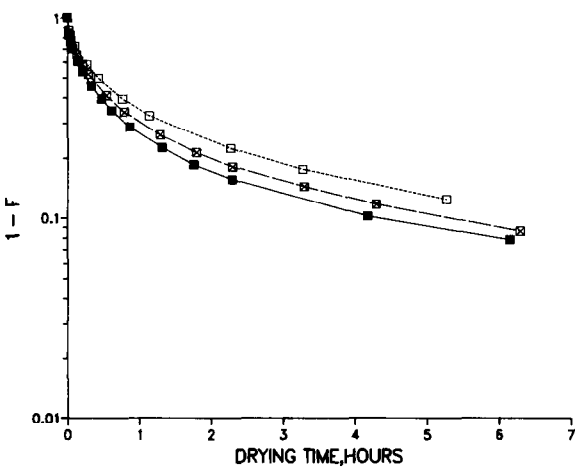

Fig. 9. Effect of initial moisture content on drying kinetics: microbalance results for formulated moxalactam di-sodium at 25°C. (□) Initial water, 2.7%; (⊠) initial water, 4.2%; (■) initial water, 7.0%.

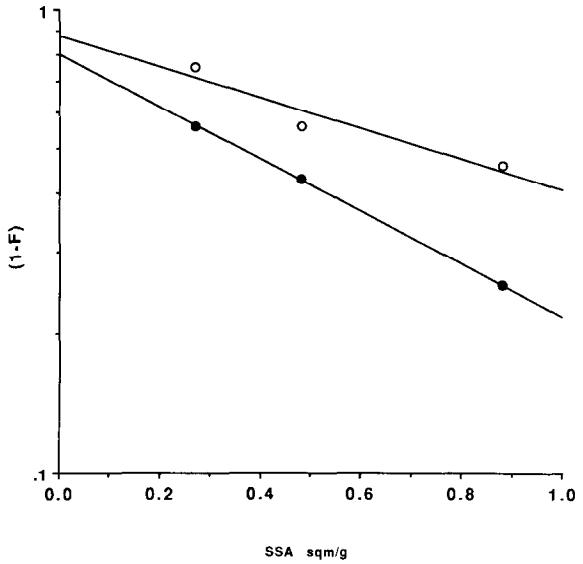

Fig. 10. Effect of specific surface area on drying kinetics of formulated moxalactam di-sodium at 18°C: vial results. (○) $(1-F)$ at 1 h, (●) $(1-F)$ at 5 h.

fill volume, which normally lowers both the degree of supercooling and freezing rate, normally decreases the specific surface area of the freeze dried product. These generalizations are valid for moxalactam di-sodium, and samples of three distinct specific surface areas were studied: 0.27 ± 0.03 m^2/g (30% solids, 8 ml fill volume), 0.48 ± 0.02 m^2/g (30% solids, 4 ml fill volume), and 0.88 ± 0.14 m^2/g (5% solids, 4 ml fill volume). Fig. 10 shows the correlation between extent of drying, measured by $1-F$, and moxalactam di-sodium specific surface area. The data represent the mean of vial data at low and high pressure with the 5 h data calculated from the mean of the 4 and 6 h $1-F$ values. The correlation is excellent with the extent of dryness increasing as the product specific surface area increases. Note that although the lowest surface area sample has twice the cake thickness as the other two samples, the values of $1-F$ for this sample do not deviate significantly from the trend with surface area established by the other two samples. Thus, cake thickness of moxalactam di-sodium does not appear to affect drying kinetics strongly.

The specific surface areas of 5% povidone freeze dried from an 8 ml fill volume (2.5 ± 0.6 m^2/g) are essentially the same as 5% povidone freeze dried from a 4 ml fill volume (2.3 ± 0.4 m^2/g). Thus, with povidone, a comparison of the 4 ml fill volume samples (1 cm cake thickness) with the 8 ml fill volume samples (2 cm cake thickness) provides a test of the effect of cake thickness on drying kinetics at constant specific surface area. The mean ratio of normalized residual water, $(1-F)_{2cm}/(1-F)_{1cm}$, is 1.19 with a standard error of ± 0.17. Thus, it appears that cake thickness is not a significant variable in secondary drying kinetics of povidone.

Discussion

Effect of process variables

Contrary to popular practice, conducting secondary drying at very low pressures does not increase the rate of drying. At least up to 0.2 mmHg, drying rate is independent of chamber pressure for each of the freeze dried products investigated. An increase of background air pressure in the microbalance freeze drying apparatus during primary drying of frozen aqueous povidone (Pikal et al., 1983a) does retard drying measurably (about 50% decrease in primary drying rate between 0 and 0.2 mmHg). These observations taken together suggest that water transport in the vapor state is not rate limiting in the secondary drying experiments conducted in this research. While early studies (Robson and Rowe, 1960; Saravacos and Stinchfield, 1967; King, 1968; Mellor, 1978) indicated the rate of secondary drying is slowed by increases in chamber pressure, this early data is not necessarily in conflict with the results generated in this research. Most of these studies (Saravacos and Stinchfield, 1967; King, 1968; Mellor, 1978) dealt with food products where the chamber pressures are considerably higher than the high pressure studied in this report (0.2 mm Hg). Indeed, the data of Saravacos and Stinchfield (reported in their Fig. 12) show very little effect of chamber pressure on drying rate of either potato or starch gel below chamber pressures of approx. 0.5 mmHg. The study by Robson and Rowe indi-

cated that, in their apparatus, the drying rate was much faster at low pressure (0.02 mmHg) than when an air leak was introduced near the pump to bring the total pressure to 0.3 mmHg. However, as the authors conclude, the apparatus itself was likely limiting mass transfer, and therefore, generalization of these results to more conventional freeze drying equipment is questionable.

The time required to achieve a given level of residual water decreases sharply as the product temperature increases. Indeed, the plateau effect kinetics suggest one could not achieve a low level of residual moisture in the product by drying at low temperature, regardless of the time of drying. While high temperatures during secondary drying are typically avoided in an attempt to minimize decomposition during the freeze drying process, one should recognize that use of high temperature to achieve a target level of residual moisture does not necessarily result in more decomposition than use of a more moderate temperature. While the chemical decomposition rate obviously increases with an increase in temperature, the time required for drying decreases with an increase in temperature. If the time of drying decreases with increasing temperature as fast as the chemical decomposition rate increases (ie., activation energy for drying is the same as activation energy for decomposition), the extent of decomposition during drying to a fixed level of residual moisture is independent of the secondary drying temperature. Such is nearly the case for moxalactam di-sodium. The activation energy for decomposition is ≈ 21 kcal/mol (Pikal et al., 1989) while that for drying is ≈ 19 kcal/mol (under Results). Thus, the in-process decomposition of moxalactam di-sodium during secondary drying is roughly independent of the temperature used, and a secondary drying process using high temperature ($\approx 55\,^{\circ}$C) leads to no more decomposition than a process using lower temperature for a longer time but has obvious advantages in process efficiency.

Since the drying rate increases with an increase in product specific surface area, process variations that may affect surface area may also significantly affect secondary drying times. Specifically, as the concentration of solution being freeze dried decreases or as the rate of freezing increases, the time required to achieve a target level of residual water during secondary drying at a given temperature will decrease. While rapid freezing is expected to yield faster secondary drying, the smaller 'pores' produced by rapid freezing will generally result in slower primary drying due to decreased rate of vapor transport through narrow 'pores' (Pikal et al., 1983a). Thus, for products that have both long primary and secondary drying times, the overall process economics may be optimum for an intermediate rate of freezing.

The observed surface area dependence of secondary drying also has implications for the mechanism of secondary drying. If the rate-limiting step in secondary drying involves transport of water vapor through the pore structure of the freeze dried solid, for the same reasons that primary drying is slower in a system of small pores (and large specific surface area), secondary drying would be slower in samples of small pores and high surface area. The observation that secondary drying is faster is moxalactam di-sodium systems of small 'pores' and high surface area implies that, at least for moxalactam di-sodium, vapor phase transport is not rate limiting in secondary drying. The observation that, at constant specific surface area, drying kinetics for both moxalactam di-sodium and povidone are insensitive to cake thickness supports this conclusion.

Mechanism of secondary drying and the origin of plateau effect kinetics

The physical state of water in amorphous systems

The physical state of the water in hydrophilic amorphous systems is generally regarded as being molecularly dispersed or dissolved in the amorphous phase, essentially forming a solid solution of water in the glassy amorphous phase (Zografi and Kontny, 1986; Levine and Slade, 1988). Evidence for this viewpoint includes the following observations: (1) such amorphous solids sorb a great deal more water than would be consistent with the specific surface area as measured by adsorption of a non-soluble gas such as nitrogen or argon. Alternatively, the specific surface area measured by sorption of water is orders of magnitude greater than the corresponding surface area as measured by nitrogen adsorption. This

observation is valid for both moxalactam di-sodium (Fig. 3) and povidone (MacKenzie and Rasmussen, 1972); (2) the solids are 'plasticized' by sorption of water, thereby reducing the glass transition temperature of the amorphous phase. Again, this observation is valid for both moxalactam di-sodium (Pikal and Shah, 1990) and povidone (MacKenzie and Rasmussen, 1972); (3) NMR relaxation times indicate that, at least at the moderate and low water contents of relevance to the secondary drying kinetics presented in this research, the environment of water is very much 'solid like', indicating strong interaction with the amorphous solid. That is, most of the water is not in a liquid state adsorbed on the surface of amorphous 'particle' nor occluded in aqueous phase 'pockets'. Pulsed proton NMR studies with moxalactam di-sodium in our laboratories (unpublished data) indicate a solid-like environment for water in moxalactam di-sodium at least up to 8% water. Therefore, we assume that in the povidone and moxalactam di-sodium systems studied, the water is 'dissolved' in the glassy amorphous phase.

The rate determining step Potential rate-determining steps in the removal of water from an amorphous solid are: (1) molecular diffusion of water in the glassy solid from the interior of a particle to the surface; (2) evaporation at the solid/vapor interface; (3) vapor phase transport through the porous dried cake; (4) vapor phase transport from headspace in the vial to the condenser. The lack of a significant cake thickness effect on drying rate is evidence that vapor phase transport in the dried cake is not rate limiting. The lack of a chamber pressure effect on drying rate, and the increase in drying rate as specific surface area increases also indicate that mass transfer in the vapor state is not rate limiting. In short, neither the apparatus nor the pore system in the dried product is rate limiting for secondary drying, at least for povidone or moxalactam di-sodium, and the rate-determining step must be controlled by the solid. However, whether diffusion through the solid, evaporation from the solid, or a combination of both mechanisms are rate determining cannot be ascertained from the data presented to this point.

In principle, the question of which solid-state mechanism is controlling can be answered by studying the initial rates of drying and water sorption. Near time zero, the semi-infinite medium approximation for the amorphous particles is appropriate within the context of diffusion theory (Crank, 1956). For the case of surface evaporation control (or surface condensation during sorption), the rate of mass transfer near zero time may be written in the form (Crank, 1956),

$$\frac{1}{m_0}\cdot\frac{\mathrm{d}m}{\mathrm{d}t} = R_s^0\left[1 - 2\sqrt{\frac{R_s^0 L}{\pi}}\sqrt{t} + Kt\right] \qquad (1)$$

where m and m_0 denote the mass of water in the sample at time t and time zero, respectively, R_s^0 is the relative surface evaporation rate, $\mathrm{d}(m/m_0)/\mathrm{d}t$, at time zero, K is a positive constant, and L is the ratio of the initial relative surface evaporation (or condensation) rate to the diffusion 'rate': $L = R_s^0/(D/l^2)$. Here, D is the diffusion coefficient of water in the amorphous particle of half-thickness, l. Thus, if drying is largely controlled by surface evaporation, the relative drying rate decreases linearly with square root of time at small times with the slope providing a measure of L and, therefore, also a measure of the diffusion coefficient, D. Conversely, if L is very large, equilibrium exists between the water in the surface region of the solid and the vapor, and diffusion in the solid becomes rate limiting. Diffusion theory (Crank, 1956) then leads to the expression,

$$\left(\frac{1}{m_0}\cdot\frac{\mathrm{d}m}{\mathrm{d}t}\right)\sqrt{t} = \sqrt{\frac{D}{\pi l^2}}\left[1 - 8\cdot F\left(\frac{Dt}{l^2}\right)\right],$$

$$F(x) = \frac{\exp\left(-\frac{1}{x}\right)}{x} \qquad (2)$$

The function, $F(x)$ is essentially zero for small x. Since $x = Dt/l^2$, x is small near zero time, and the product of the relative drying rate (or water sorption rate) and square root of time should be essentially a constant near zero time, and should decrease with time at later times – provided solid-state diffusion is rate limiting.

Using microbalance data for formulated moxalactam di-sodium accumulated very early in the

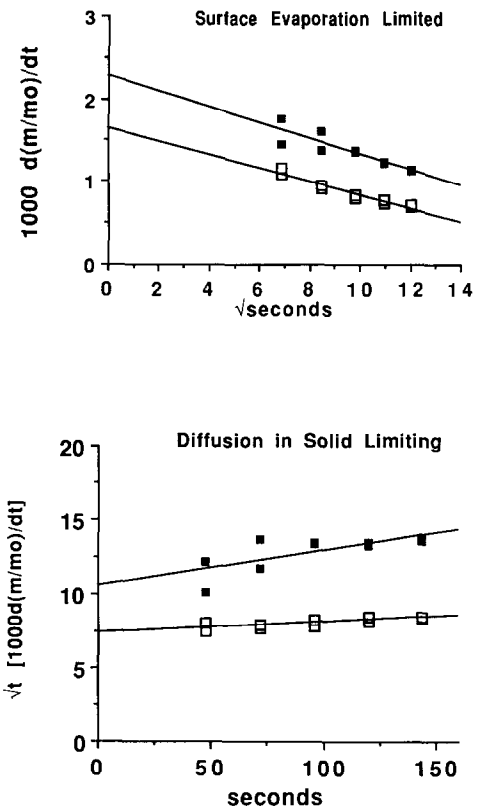

Fig. 11. Analysis of drying rate and sorption rate near time zero and implications for mass transfer mechanism: microbalance data for formulated moxalactam di-sodium at 25° C. (□) Drying, (■) sorption.

experiments, rate data resulting from two replicate drying experiments (open symbols) and two replicate sorption experiments (filled symbols) are plotted according to Eqn 1 (surface evaporation limited) in the upper panel of Fig. 11 and plotted according to Eqn 2 (solid-state diffusion limited) in the lower panel. Note that the sorption rate is higher than the drying rate. This is likely the result of the sample temperature being several degrees cooler during early drying than during early sorption (see Experimental). As required by theory, the 'surface evaporation limited' plot shows a decrease in mass transfer which is roughly linear in square root of time. Calculation of the diffusion coefficient from the slope and intercept requires an estimate for the half-thickness of the amorphous particle, l, whose geometry is approximated as a slab. With this model, the value of l may be related to the product density, ρ_s, and the product specific surface area in cm^2/g, S': $l = 1/\rho_s S'$. While the specific surface area of this moxalactam di-sodium sample was not measured, by use of the correlation between surface area and drying kinetics established in Fig. 10, the specific surface area is estimated as 1.3 m^2/g. With $\rho_s \approx 1.5$ g/cm^3, the calculated value of half-thickness is, $l \approx 5.1 \times 10^{-5}$ cm. The mean diffusion coefficient calculated from the slope and intercept is then $\approx 7 \times 10^{-12}$ cm^2/s.

Theoretically, the 'diffusion in solid limiting' plot should show a constant ordinate, with perhaps a decrease at longer times. The ordinate is nearly constant but shows a small increase with time for both sorption and desorption. However, this increase with time is slight and could be the result of systematic experimental error. The mean diffusion coefficient calculated from the intercepts is 8×10^{-13} cm^2/s. Since the diffusion coefficient of water in low moisture glassy epoxide prepolymers is approx. 10^{-10} cm^2/s (Garcia-Fierro and Aleman, 1985), one would expect a diffusion coefficient of this general magnitude for water in moxalactam di-sodium. The diffusion coefficient calculated assuming surface evaporation limited mass transfer is more consistent with this expectation. Thus, while the correspondence between theory and experiment shown by the analysis in Fig. 11 favors surface evaporation as rate limiting, the analysis is far from definitive. A study (Pikal and Shah, 1990) of drying kinetics of glassy moxalactam in slab geometry ($l \approx 0.2$ mm, surface area ≈ 0.5 cm^2) indicates that drying is surface evaporation controlled under conditions of low temperature (≈ -20° C) and high water content (0.26 g/cm^3). While extrapolation of these observations to the higher temperatures and lower water contents relevant to secondary drying studies is not rigorous, such an extrapolation is plausible. Thus, we tentatively conclude that mass transfer during secondary drying is controlled by surface evaporation.

Particle size heterogeneity and drying kinetics: A theoretical model Here, we will show that diffusion theory with surface evaporation control is qualitatively consistent with plateau effect drying kinetics, provided one assumes particle size het-

erogeneity in the amorphous solid. We assume Fickian diffusion with a constant diffusion coefficient and employ a surface evaporation boundary condition (Crank, 1956). The freeze dried cake is assumed to be equivalent to a system of connected particles, each having slab geometry and the same mass. The thickness of a given particle is $2l$, where l is variable, depending on the particle considered.

The surface evaporation boundary condition is (Crank, 1956),

$$J = D\left(\frac{\partial c}{\partial x}\right)_s = k_R P_S \tag{3}$$

where J is the molar water flux from the slab surface, D is the diffusion coefficient of water in the amorphous system, c is the concentration of water in the solid (a function of time and distance, x), and k_R is a constant which measures the rate of evaporation from the surface but could also depend on the resistance of the pore system to water vapor transport. The partial pressure of water which would be in equilibrium with the concentration of water at the surface is denoted, P_s, and the subscript, s on the concentration gradient indicates this derivative is evaluated at the surface of the particle. To relate partial pressure of water to water concentration in the solid, we assume Henry's law, $P_s = k_H c_s$, which then gives, $D(\partial c/\partial x)_s = \alpha c_s$, with $\alpha = k_H k_R$. While it is obvious from the data (Fig. 3) that Henry's law is only a crude first approximation, this form of estimation is necessary to simplify the mathematics.

The actual particle size heterogeneity is approximated by assuming a continuous distribution of equivalent slab half-thickness, l. Specifically, we arbitrarily assume that the reciprocal of slab half-thickness is normally distributed, which is equivalent to assuming the specific surface area of the particles is normally distributed. Thus, the number fraction of particles, dN/N, with reciprocal half-thickness between $1/l$ and $1/l + d(1/l)$ is,

$$\frac{dN}{N} = k \exp\left[-\left(\frac{l^{-1} - \mu}{\sqrt{2}\sigma}\right)^2\right] d(l^{-1}) \tag{4}$$

where μ is the mean value of $1/l$, and σ is the standard deviation in $1/l$. The normalization constant, k, is evaluated by integrating Eqn 4 over all values of l $(0-\infty)$ with the condition, $\int_l dN/N = 1$, giving

$$k = \left\{\sigma\sqrt{\frac{\pi}{2}}\left[1 + \operatorname{erf}\left(\frac{\mu}{\sqrt{2}\sigma}\right)\right]\right\}^{-1} \tag{5}$$

where erf denotes the error function. For a given particle, i, of thickness $2l$, the mass of water desorbed, M_t^i, relative to that desorbed at time infinity, M_∞^i, is (Crank, 1956)

$$\frac{M_t^i}{M_\infty^i} = 1 - \exp\left(-\frac{\alpha}{l}t\right); \ldots \frac{\alpha l}{D} \leq 5 \tag{6}$$

where the condition, $\alpha l/D \leq 5$, restricts the expression to the case of surface evaporation mass transfer control. While this restriction is consistent with our tentative conclusions reached earlier, it should be noted that the opposite situation of solid state diffusion control leads to an expression of similar form at times long enough to give more than about 20% loss in moisture, $M_t^i/M_\infty^i \approx 1 - 0.81 \exp(-\pi^2 Dt/4l^2)$. Thus, assumption of solid state diffusion control would lead to qualitatively the same kinetics as those derived from Eqn 6, the results being particularly close if $1/l^2$ were assumed to be normally distributed. Noting that since all particles are of the same mass, M_∞^i is the same for all particles, which we denote by, M_∞. The total water loss from all particles at time t, M_t, is then obtained by summing the contributions from each particle, using Eqn 4 to evaluate the fraction of particles in each size range and Eqn 6 for the kinetics for each particle, giving

$$1 - F = 1 - \frac{M_t}{M_\infty}$$

$$= k\int_0^\infty \exp\left(-\frac{\alpha}{l}t\right) \exp\left[-\frac{(l^{-1} - \mu)^2}{2\sigma^2}\right] d(l^{-1}) \tag{7}$$

Performing the indicated integration and using Eqn 5 for k then gives the final result,

$$1 - F = \frac{\exp\left[-at(1 - b^2at)\right]\ \mathrm{erfc}(bat - 1/2b)}{1 + \mathrm{erf}(1/2b)} \tag{8}$$

where erfc is the error function complement, $\mathrm{erfc}(x) = 1 - \mathrm{erf}(x)$. The parameter, a, is the initial evaporation rate, $a = \alpha\langle l^{-1}\rangle$, where $\langle l^{-1}\rangle$ denotes the mean value of $1/l$. The parameter, b, is a measure of the relative variation in $1/l$, and is defined as

$$b = \frac{1}{\sqrt{2}} \frac{\sigma(1/l)}{\langle 1/l\rangle} \tag{9}$$

Note that since the specific surface area of the sample is directly proportional to the mean value of $1/l$, the parameters, a and b involve the mean particle specific surface area and variation in particle surface area, respectively.

The type of drying kinetics predicted by Eqn 8 is shown in Fig. 12. The straight line (semi-log plot) gives the result for a homogeneous particle system ($b = 0$). The dashed line showing curvature

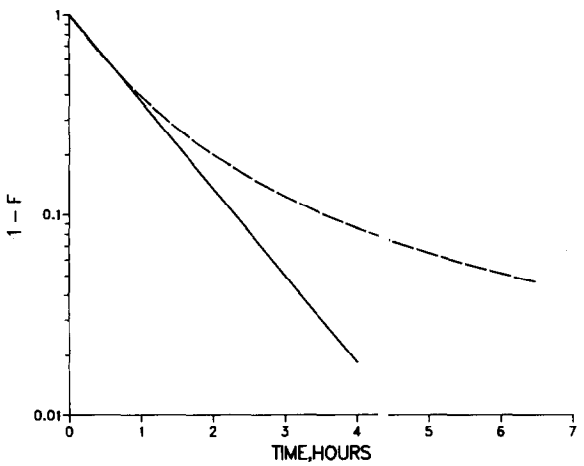

Fig. 12. Effect of particle size heterogeneity on drying kinetics: theoretical results. (———) Homogeneous particle system with the parameter, $a = 1.0$; (— — —) heterogeneous particle system with parameters, $a = 1.0$, $= 0.5$.

similar to that shown by drying data was calculated for $b = 0.5$. A higher value of b, indicating greater heterogeneity, would give more curvature. Thus, we conclude that particle size heterogeneity in the amorphous solid is, at least in part, responsible for the plateau effect kinetics observed in the secondary drying of moxalactam di-sodium and povidone.

Conclusions

Drying kinetics are characterized by a rapid loss of water initially, followed by slower drying where the residual water appears to approach a plateau level, which for amorphous materials can represent significant quantities of residual water. The observed kinetics are due, at least in part, to heterogeneity in thickness of the amorphous particles comprising the freeze dried solid. The plateau level of residual water decreases sharply as the drying temperature increases, and in practice, the attainment of low levels of residual water may demand high secondary drying temperatures. Drying rate increases as the product specific surface area increases, and at constant surface area, is relatively independent of dried cake thickness. Contrary to common opinion, the rate of secondary drying does not depend on the chamber pressure in the range of pressures normally encountered in freeze drying of pharmaceuticals (0–0.2 mmHg). Thus, the common practice of reducing the pressure to 'as low as possible' during secondary drying is without sound foundation. Indeed, higher chamber pressure during secondary drying can be an advantage when transfer of stopper components to the product is a problem (Pikal and Lang, 1978). Also, in some applications, particularly involving 'bulk' solution freeze drying in pans, formation of 'islands of ice' may occur (i.e., residual ice completely surrounded by low thermal conductivity dried product). In such cases, primary drying may appear complete, but even after the secondary drying stage conducted at very low pressure, residual ice may persist which then melts when the product is removed from the freeze dryer. Here, due to increasing thermal conductivity in the dried cake as pressure increases,

complete ice removal is accelerated by using higher chamber pressure (Mellor, 1978).

References

Crank, J.H., *The Mathematics of Diffusion*, Oxford University Press, 1956, p. 56.

Garcia-Fierro, J.L. and Aleman, J.V., Diffusion of water in glassy epoxide prepolymers. *Polym. Eng. Sci.*, 25 (1985) 419–424.

King, C.J., Rates of moisture sorption and desorption in porous, dried foodstuffs. *Food Technol.*, 22 (1968) 165–171.

Levine, H. and Slade, L., Principles of cryostabilization technology from structure property relationships of carbohydrate/water systems: A review. *Cryo-Letters*, 9 (1988) 21–63.

MacKenzie, A.P. and Rasmussen, D.H., Interactions in the water-polyvinylpyrrolidone system at low temperatures. In Jellinek, H.H.G. (Ed.), *Water Structure at the Water-Polymer Interface*, Plenum, New York, 1972, pp. 146–172.

Mellor, J.D., *Fundamentals of Freeze-Drying*, Academic Press, London, 1978.

Nail, S., The effect of chamber pressure on heat transfer in the freeze drying of parenteral solutions. *J. Parent. Drug Assoc.*, 34 (1980) 358–368.

Pikal, M.J., Use of laboratory data in freeze drying process design: Heat and mass transfer coefficients and the computer simulation of freeze drying. *J. Parent. Sci. Technol.*, 39 (1985) 115–138.

Pikal, M.J. and Shah, S., The collapse temperature in freeze drying: Dependence on measurement methodology and rate of water removal from the glassy phase. *Int. J. Pharm.* (1990) in press.

Pikal, M.J. and Lang, J.E., Rubber closures as a source of haze in freeze dried parenterals: Test methodology for closure evaluation. *J. Parent. Drug Assoc.*, 32 (1978) 162–173.

Pikal, M.J., Roy, M.L. and Shah, S., Mass and heat transfer in vial freeze-drying of pharmaceuticals: Role of the vial. *J. Pharm. Sci.*, 73 (1984) 1224–1237.

Pikal, M.J., Shah, S., Senior, D. and Lang, J.E., Physical chemistry of freeze-drying: measurement of sublimation rates for frozen aqueous solutions by a microbalance technique. *J. Pharm. Sci.*, 72 (1983a) 635–650.

Pikal, M.J., Lang, J.E. and Shah, S., Desolvation kinetics of cefamandole sodium methanolate: The effect of water vapor. *Int. J. Pharm., 17* (1983b) 237–262.

Pikal, M.J. and Dellerman, K.M., Stability testing of pharmaceuticals by high-sensitivity isothermal calorimetry at 25°C: cephalosporins in the solid and aqueous solution states. *Int. J. Pharm.*, 50 (1989) 233–252.

Robson, E.M. and Rowe, T.W.G., The physics of secondary drying. In Parkes, A.S. and Smith, A.U. (Eds), *Recent Research in Freezing and Drying*, Blackwell, Oxford, 1960, pp. 146–166.

Saravacos, G.D. and Stinchfield, R.M., Effect of temperature and pressure on the sorption of water vapor by freeze-dried food materials. *J. Food Sci.*, 30 (1967) 779–786.

Zografi, G. and Kontny, M., The interactions of water with cellulose- and starch-derived pharmaceutical excipients. *Pharm. Res.*, 3 (1986) 187–194.